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NEPHROCALCINOSIS IN CHILDREN

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Abstract:

Objectives: To study the data of children with Nephrocalcinosis (NC) and to analyze etiology, presenting complaints, clinical findings, growth and development, renal function at presentation, treatment, and to relate growth and renal function to changes in NC in patients with a follow-up for a period of at least of 36 months.

Methods: Twenty-five patients were diagnosed with NC in the nephrology unit of our hospital, but only eighteen of them were followed during this study. These patients were evaluated prospectively.

Results: Current symptoms were failure to thrive in the first year of life (67%)., urinary tract infections, bladder voiding dysfunction or abdominal pain (22%). In 11% of cases NC was detected accidentally. Renal function at diagnosis was normal in 83% of children. During a follow-up of 36 months of 18 patients, growth standard score improved from a median of -2,2 to -1,0, in spite of worsening of the degree of NC. The most frequent causes of NC were hereditary tubulopathy and vitamin D intoxication in childhood in Albania.

Conclusion: Our results show that the treatment of the underlying conditions is associated with catch-up growth and stabilization of renal function in many children, but not with reduction in the degree of NC in the majority of cases. We believe that early recognition of conditions leading to NC is clinically useful and suggest a diagnostic flowchart, which may be helpful in the approach to NC.

INTRODUCTION

Since ultrasound was introduced as a routine diagnostic procedure, nephrocalcinosis (NC) has been increasingly detected in both children and adults, and diseases sassociated with NC have also been diagnosed. Furthermore, up to 60% of prematurely born children (gestational age <32 weeks) develop NC, with long-term consequences for glomerular and tubular function (low plasma bicarbonate and high urine calcium/citrate ratio [1]. The new classification proposed for NC is based on ultrasound appearance and distinguishes medullary, cortical, and global NC [2]. In addition, Hoyer [2], Patriquin and Robitaille [3] introduced ultrasound grading of medullary hyperechogenicity in four types. It has also been stated that whether NC is harmful or not depends on whether it is the result of an ongoing problem or of a transitory insult, and not because of its magnitude [4].

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However, few longitudinal studies are performed in children. Although some series of NC in children diagnosed by ultrasonography have been published [5-9], we have distinguished only two main studies that describe a longitudinal follow-up: one retrospective multi-center study (152 children and adolescents) performed in Germany [8] and a single center study of 40 childrenin India [9]. In the study conducted in Germany, patients with primary hyperoxaluria were not included. The most common frequent diseases associated with NC were hereditary tubular disorders and idiopathic hypercalciuria (IH); growth retardation was observed in approximately half of the patients while severe impairment of renal function was rarely observed and no patient developedend stage renal insufficiency. In the study conducted in India, the etiology of NC included distal renal tubular acidosis (dRTA) in 50% of patients and IH and hyperoxaluria in 7.5% each. After a median follow-up of 35 months, glomerular filtration rate (GFR) was decreased by 15%, and most patients continued to show growth retardation and none resolution of NC. The aim of our study was the prospective evaluation of the clinical presentation and diagnosis of children with NC, excluding those related to prematurity; assessment of growth and renal function in relation to the evolution of ultrasound data and bio-humoral corrections during follow-up. We also propose a flowchart for the diagnostic approach in children with NC.

MATERIAL AND METHODS

Data on patients followed in our unit were retrospectively analysed: the records of 18 children with a US diagnosis of bilateral NC were reviewed at Pediatrics department of the University Hospital Center “Mother Teresa”, in Tirana, Albania, which represents III level referral center for nephrological problems in our country.

Premature infants and neonates treated with furosemide with a diagnosis of NC were not included in the study. The evaluated parameters at the time of presentation for each patient were: clinical manifestations, body height and weight, urinary calcium excretion, glomerular function, renal US. Auxological data were analysed using Tanner／Whitehouse tables, and the height standard deviation score (SDS) was calculated using the standards of Tanner, Whitehouse, and Takaishi [10]. Glomerular function estimated as GFR, calculated by the Schwartz formula, in children older than 1 year (11), and it was considered normal if its value was >80 mL／min／1.73 m^2; in children younger than 1 year, a table of age specific limits for serum creatinine, as mean ± 3 SD was used. Calciuria was calculated by the urinary calcium / creatinine ratio (Ca／Cr) in second morning urine samples or in mg/ kg／day.

The values of Matos et al. (12) were used as references for the Ca / Cr ratio, and values> 4 mg/ kg / day were considered high in the urine collected within 24 hours. Diagnosis of the most common conditions was made as follows: Drta by a positive urinary gap anion and high urinary pH in the presence of hyperchloremic metabolic acidosis; vitamin D (VD) intoxication by hypercalcemic-hypercalciuria with low levels of parathyroid hormone,high plasma VD levels and corresponding clinical history. Type I hyperoxaluria was confirmed by molecular analysis in the presence of suggestive clinical data and increased plasma oxalate levels. US was performed in the Department of Pediatrics in the Nephrology and Radiology Unit, with 3.5–5 MHz convex probes.

Out of 25 patients in total, 18 of them were followed for at least 36 months. Growth, glomerular function and evolution of NC, were analysed at last examination and compared with data at presentation.

RESULTS AND DISCUSSION

Baseline data

Age of 18 (12 males and 6 females) patients at first examination varied from 15 days to 10 years old (median 15 months). Signs and symptoms which brought children to medical attention were: failure to thrive in first year of life in 67% of children; urinary tract infections, bladder voiding dysfunction or recurrent abdominal pain in 22% of children; a miscellany ofsigns or symptoms was present in 7% of children. NC was detected accidentally in 11% of the cases during screenings or follow-upin congenital syndromes or malformations. 55% of children showed height below the third percentile. Glomerular function was normal in the great majority (83%) of patients, two children suffered from renal insufficiency (GFR from 24 and 68 mL/ min / 1.73 m^2) and one 10 years old child was accidentallydiagnosed only at presentation with terminal renal failure. Hypercalciuria was found in 44% of patients. In 61% of children, NC was associated with hereditary tubulopathy and in 11% of cases secondary to VD intoxication. Other causes and details are shown in Table 1.In 11% of children the cause of NC remained unknown. NC was classified as medullary in 89% of patients and global in 11%. Global NC was detected in two children: one suffered from terminal renal failure and the other from oxalosis.

Follow-up

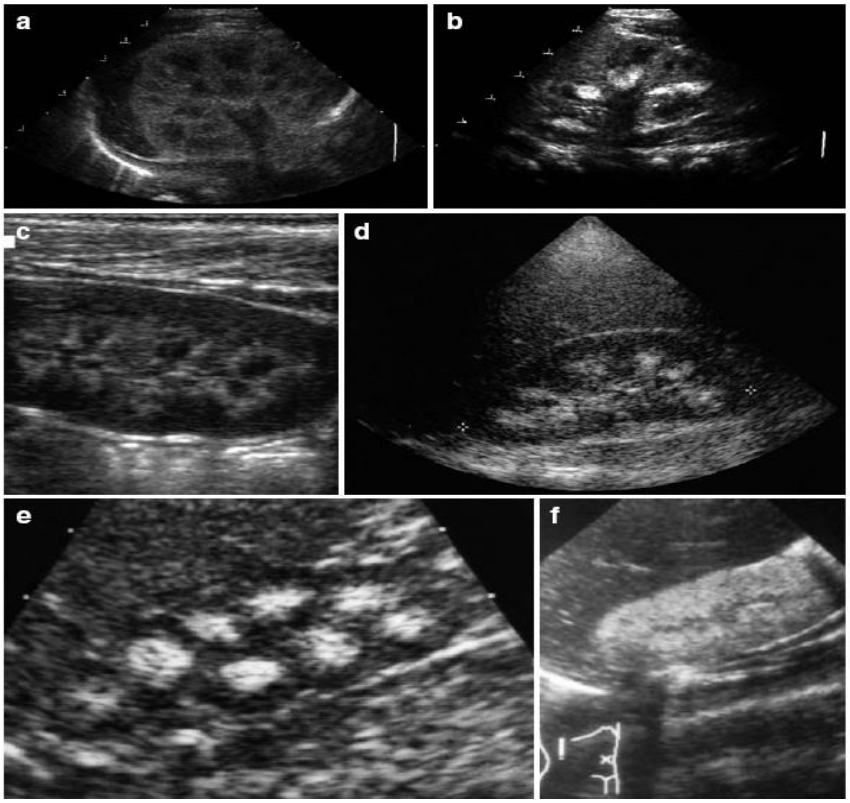
Data of 18 / 25 patients (12 males and 6 females) followed for at least 36 months were analyzed:detailed diagnosis arerepresented in Table 1. In these patients, SDS for height improved from a median value of -2.2 (range -6.8. +1.1) to a median value of -1.0 (range -3.2

/+2.4) at the end offollow-up. Heigh was below -2.0 SDS in 54% of children at presentation and in 22% at last investigation. Among the 11 patientswhose growth improved, there were 7/8 children with dRTA, Bartter syndrome and Dent disease. None of the patients had been treated with growth hormone at any time during follow-up. In 7/18 children >1 year old GFR was decreased in 57%atpresentation and in 14% at follow-up. In particular, remarkable improvement of glomerular function was observed in one child with VD intoxication, after withdrawal of the drug, and in one child who suffered from Dent disease after stone removal; a decreasing GFR was confirmed and remained so only in the patientsuffering from terminal renal failure.

The degree of NC (follow-up for 18 patients) worsened in 9 patients (50%), remained stable in 5 (28%) and decreased in 4 patients (22%). In particular, NC worsened in children with Bartter syndrome and Dent disease in whom growth was improved; the same was true for 4/8 patients with dRTA. Of the four children in whom improvement of NC was observed, two suffered from dRTA, one from VD intoxication and the other one from an unknown cause. We found no relation between glomerular function and worsening of NC, as GFR remained stable in 17/18 patients showing progression of NC.

Table1. Underlying conditions in children with NC at baseline and at follow-up

Condition	**No. of patients**	**No. of patients with follow-up>36 months**
Distal renal tubular acidosis	11	8
Other hereditary tubulopathies: Bartter syndrome Dent disease	3 1 1	3 1 1
Hyperoxaluria type I	1	1
Idiopathic hypercalciuria	2	2
Vitamin D intoxication	4	4
Hypercalcemia with hypercalciuria	1	1
Unknown	4	2
Total	25	18



The results of this study have been gathered retrospectively from the records of Pediatric Nephrology Department, located in the University Hospital Center of Tirana "Mother Teresa", which represents III level referral center for nephrological problems in our country. AsNC is an uncommon disease, which is not usually looked after by general pediatric departmentsin our country and is therefore referredin our center, we expect that the spectrum of diagnoses, in our cohort of children, reflects the epidemiology of NC of the area.

Urinary tract infections, bladder voiding dysfunction or abdominal pain also brought children to medical attention. To the best of our knowledge, clinical manifestations and especially somatic and psychomotor development had not been examined in significant studies in children with NC detected by US until the study of Rönnefarth et al. [8].In this study, growth failure, psychomotor and mental retardation were found in a high percentage of patients; in particular, height below the lower normal limit was detected at presentation in 41% of 72 children older than 1 year. In addition, more than one third of their patients suffered from urinary tract infections. Growth improved during clinical follow-up in 61% of children in our study, especially in patients with dRTA, Bartter syndrome, and Dent disease.In the German study [8], significant growth improvement was only observed in patients with IH, but a relative improvement was also stated in some patients suffering from tubular disorders as well as in patients who had received bolus prophylaxis or prolonged VD therapy. In the

Indian study, most patients continued to show growth retardation and GFR declined by 15% after a median follow-up of approximately 35 months [9]. Glomerular function was normal in most of our cases, except for three children; one with oxalosis, another with Dent disease and the third one showed global NC and was interminal renal failure at first examination. In the case of global NC, a rare ultrasound parameter often related to oxalosis, the search for this conditionappears mandatory.

Our follow-up data on GFR in patients older than 1 year of age are similar to those of Rönnefarth et al, who found that 43% (3 of 7 patients suffering from renal insufficicieny) had a GFR less than 80 mL/ min/ 1.73 m^2 at presentation and 29% at last investigation. Therefore, improvement of GFR can be expected after an accurate diagnosis and correct treatment of the cause of NC. Our experience also shows that, unless the patients hasoxalosis or Dent disease, and provided acute insults are removed, prognosis concerning glomerular function in children with NC is good. Regression of NC should not be expected; on the contrary, worsening of NC during follow-up by US was a common finding both in our and Rönnefarth's studies, most of the cases being represented by hereditary tubulopathies. However, the available follow-up data on persistance or even progression of NC, do not present a negative prognostic factor for growth and renal function. It is not beneficial to continue describing drug induced NC in every study [5-9]; it is often secondary to VD intoxication or treatment, especially in countries where bolus administration of high doses has been used.In our study, four patients developed NC, which was permanent in two, after hypercalcemic-hypercalciuria due to VD treatment. Therefore, the high risk of bolus VD prophylaxis and the need for careful controls of calciuria during substitutive therapy should be acknowledged. IH was an exceptional cause of NC in our study, since it was only detected in two patients, who also presented with renal stones during their infancy. A low incidence of IH as a cause of NC was also stated in previous studies [5–7]; the German study is an exception [11], in which IH was found to be the main cause of NC, representing 34% of cases. The cause of NC could not be identified in four of our patients, two of them having been lost to follow up. In some of these cases, the diagnosis of medullary sponge kidney may have been missed, as an intravenous pyelography was not performed routinely in NC of unknown origin [12]. From the review of the clinical history and the results of the diagnostic procedures of the patients evaluated in this retrospective study and from the review of the available literature, we have produced two diagnostic flowcharts, which may be helpful in the clinical approach to NC in children.

CONCLUSION

In conclusion, our results show that treatment of the underlying conditions is assocciated with catch-up growth and stabilisation of glomerular function in many children with NC. We therefore believe that early recognition of conditions leading to NC is clinically useful. Treatment, however, does not reduce the degree of NC in the majority of cases; therefore NC seems to be an epiphenomenon having little influence on the clinical course.

REFERENCES

[1] Kist-van Holthe JE, van Zwieten PH, Schell-Feith EA, ZonderlandHM, Holscher HC, Wolterbeek R, et al. Is nephrocalcinosisin preterm neonates harmful for long-term blood pressureand renal function? Pediatrics 2007; 119: 468–75.

[2] Hoyer PF. Nephrocalcinose. In: Hofmann V, Deeg KH, HoyerPF, editors. Ultraschalldiagnostik in Pa¨ diatrie und Kinderchirurgie.Stuttgard: Thieme, 1996: 372–4.

[3] Patriquin H, Robitaille P. Renal calcium deposition in children:sonographicdemonstration of the Anderson-Carr progression.AJR 1986; 6: 1253–6.

[4] Alon US. Hypercalciuria and nephrocalcinosis. Pediatr Nephrol1998; 12: C 45.

[5] Jequier S, Kaplan BS. Echogenic renal pyramids in children.J Clin Ultrasound1991; 19: 85–92.

[6] Nayir A, Kadioglu A, Sirin A, Emre S, Tongue E, Bilge I. Causesof increased medullary ecogenicity in Turkish children. PediatrNephrol 1995; 9: 729–33.

[7] Shultz PK, Strife JL, Strife FC, McDaniel J. Hyperechoic renalmedullary pyramids in infants and children. Pediatric Radiol1991; 181: 163–7.

[8] Ro¨ nnefarth G, Misselwitz J, members of APN. Nephrocalcinosisin children: a retrospective survey. Pediatr Nephrol 2000;14: 1016–21.

[9] Mantan M, Bagga A, Virdi VS, Menon S, Hari P. Etiology ofnephrocalcinosis inchildren. Pediatr Nephrol 2007; 22: 829–33.

[10] Tanner JM, Whitehouse RH, Takaishi M. Standards from birthto maturity forheight, weight, height velocity, and weight velocity:British children, 1695 Part II. Arch Dis Child 1966; 41:613–35.

[11] Schwartz GJ, Haycock GB, Edelman CM, Spitzer A. A simpleestimate of glomerular filtration rate in children derived frombody length and plasma creatinine. Pediatrics 1976; 58:259–63.

[12] Matos V, van Melle G, Boulat O, Markers M, Bachmann C,Guignard JP. Urinary phosphate ⁄ creatinine, calcium ⁄creatinine and magnesium ⁄ creatinine in a healthy pediatricpopulation. J Pediatr 1997; 131: 252–7.